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Fc receptor homologs: newest members of a remarkably diverse Fc receptor gene family

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Summary: Newfound relatives of the classical Fc receptors (FcR) have been provisionally named the Fc receptor homologs (FcRH). The recent identification of eight human and six mouse *FcRH* genes substantially increases the size and functional potential of the FcR family. The extended family of *FcR* and *FcRH* genes spans ~15 Mb of the human chromosome 1q21–23 region, whereas in mice this family is split between chromosomes 1 and 3. The *FcRH* genes encode molecules with variable combinations of five subtypes of immunoglobulin (Ig) domains. The presence of a conserved sequence motif in one Ig domain subtype implies Ig Fc binding capability for many FcRH family members that are preferentially expressed by B lineage cells. In addition, most FcRH family members have consensus tyrosine-based activating and inhibitory motifs in their cytoplasmic domains, while the others lack features typical of transmembrane receptors. The FcRH family members, like the classical FcRs, come in multiple isoforms and allelic variations. The unique individual and polymorphic properties of the FcR/FcRH members indicate a remarkably diverse Fc receptor gene family with immunoregulatory function.

Introduction

Beginning with the initial identification of cellular immunoglobulin (Ig)-binding receptors more than 30 years ago, the field of Fc receptor (FcR) biology has evolved to a comprehensive understanding of the biological consequences resulting from the physical interactions of FcRs with the Fc portion of Ig (1–4). The early observations that linked antibodies with the *FcγRI*, *FcγRII*, *FcγRIII*, and *FcεRI* on effector cells led to the identification of complex regulatory networks that integrate innate immunity with the cell-mediated and humoral arms of adaptive immune responses (5–8). Characterization of the classical FcRs, encoded by genes in the human chromosome 1q21–23 region, includes the elucidation of genomic and amino acid sequences of multiple FcR isoforms, specific cellular expression patterns, signaling potential, polymorphic functional properties, and protein structures (9–14). Struc-

tural analysis has yielded insight into the physiochemical interactions required for Fc binding and the essential Ig binding domains that have been maintained throughout vertebrate evolution (15–20). Genetically engineered mice deficient in *FcR* genes have demonstrated the involvement of these receptors in autoimmune diseases and verified their key roles in hypersensitivity reactions (13, 21–28). While some facets of FcR function are still unresolved, it is abundantly clear that the classical FcRs play an important role in maintaining the intricate coordination and balance between cellular and humoral immunity in higher vertebrates.

Robust efforts to sequence the genomes of model organisms and the complementary analysis of expressed sequence tags (ESTs) derived from specialized tissues have led to the recent identification of many previously unrecognized genes. This information has enabled a detailed genetic analysis of the phylogenetic relatedness of large gene families. Comparative analysis of homologous genes (either orthologs or paralogs) in different organisms has shed light on their genomic relatedness and diversity and provided theoretical connections between syntenic regions and immune function. Complex loci conserved for ~500 million years of vertebrate evolution, including the major histocompatibility complex (MHC) and the rearranging B-cell and T-cell receptor gene families, are related not only by similar sequence and structure but also by shared functional relationships. Their co-evolution with other multigene families accounts for the remarkably integrated features of adaptive immunity. Such higher order relationships involving many different gene families are proving to be more common than anticipated. This is particularly true for members of the Ig-gene superfamily that encode the most common domain type in the human proteome (29, 30).

A large Ig-like gene family of *FcαR* relatives has been characterized in a human chromosome 19q13.4 region known as the leukocyte receptor cluster (LRC) of genes (31–36). This polymorphic gene family of ~26 members encodes transmembrane immunoreceptors with tyrosine-based activating and inhibitory signaling properties (37, 38). These include the FcαR (CD89) (39), Ig-like transcripts/leukocyte Ig-like receptors (ILT/LIR/MIR-CD85) (33, 40–42), natural killer Ig-like receptors (KIR/CD158) (43–46), leukocyte associated-inhibitory receptors (LAIR) (47), and NKp46 (48). The closest mouse relatives of the LRC encoded receptors are the paired Ig-like receptors (PIR) that reside in a mouse chromosome 7 region syntenic with the human chromosome 19q13.4 region (49). Interestingly, NKp46 is the only LRC member that has maintained orthologous properties in humans and mice (50). While the *ILT/LIR* genes are likely to be the closest homologs of the murine PIRs (37, 51, 52), the KIRs, which have been identified in humans and other mammals but not in mice, are thought to represent a recent independent expansion of the primate LRC (38, 53, 54).

The ligands for the immunoreceptors encoded by LRC genes are typically other members of the Ig superfamily. Many LRC Ig-like receptors, including the KIRs and LIRs, have MHC class I and class I-like ligands (17, 41, 45, 55–61). Allelic variants of the *KIR* and *LIR* genes and haplotypic differences in the numbers of these genes are manifested by differences in the receptor repertoire between individuals and even between different subsets of cells within individuals (35, 62). While the functional consequences of the polymorphic extracellular regions of these receptors are not yet fully understood, their intracellular signaling capacity is conserved among family members; their possession of common activating or inhibitory cytoplasmic signaling motifs relates the LRC receptors to a larger group of paired Ig-like receptors that regulate the activation status of the cells that bear them (63, 64). The signaling properties that distinguish inhibitory isoforms reside in their cytoplasmic tails and bestow the ability to initiate cellular inhibition via immunoreceptor tyrosine-based inhibitory motifs (ITIM) (65–67). Activating isoforms may have long cytoplasmic tails with immunoreceptor tyrosine-based activation motifs (ITAM) or, more commonly, associate with ITAM-bearing adapter proteins via non-covalent interaction of charged amino acids in their respective transmembrane regions (68–73). The associated adapter proteins include DAP12 and DAP10/KAP10 (74–78), which are encoded by genes in the region surrounding the LRC on chromosome 19, and the Fc receptor common γ chain (FcRγc) and CD3ζ chains, the genes for which are located in the region surrounding the Fc receptor genes on chromosome 1 (79–84). Notable similarities between these two clusters of Ig-like receptor genes include genomic structure, amino acid content, Ig domain ligands, and tyrosine-based signaling, features that collectively suggest a shared phylogenetic background.

Identification of Fc receptor homologs

The large number of *FcαR* relatives in the LRC gene family suggested to us that an extended family of the classical Fc receptors might exist within the chromosome 1q21–23 region. Utilizing available sequence information, we identified an amino acid (aa) consensus sequence derived from the second domains of human FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16), and the third domain of polymeric Ig recep-

tor. When this 32 aa motif was used in a Genbank database query, genomic clones from the 1q21–22 region were identified that contained five Ig superfamily members, which we have provisionally termed the Fc receptor homolog family (*huFcRH1-5*) (85, 86). Identification of ESTs in the Lymphochip database (87) inferred B-cell expression for many of these genes, an implication that is supported by RNA blot and reverse-transcriptase polymerase chain reaction (RT-PCR) analyses (85). The *FcRH1-5* genes were independently identified as immunoglobulin superfamily receptor translocation associated genes (*IRTA*) through an analysis of the breakpoints of a t(1;14)(q21;q32) chromosomal translocation from a multiple myeloma cell line (88, 89). Others have identified members of this family as *IFGP* (IgSF, FcR, gp42) (90) and *SPAP* (SH2 domain-containing phosphatase anchor protein) genes (91). Further analysis with the FcR consensus motif and amino acid sequences, which include huFcRH1-5 specific Ig-like domains and the third Ig domain (D3) of huFcγRI, led to the identification of an Fc receptor related gene, *huFcRX/FcRL/FREB*, and its mouse ortholog, *moFcRX* (92–94). A similar database analysis has since identified additional novel *FcRH* family members in both humans and mice (see *Fig. 1*). The recognition of this extensive family of Fc receptor relatives reveals a previously unanticipated diversity for the Fc receptor family.

Genomic diversity of the Fc receptor cluster

In parallel with the LRC family members, the classical Fc receptors and the FcRHs are related by chromosomal proximity and genomic structure. The specific organization of these genes is provisional, but data from the public and private databases suggests the Fc Receptor Cluster (FRC) spans over 15 Mb in the human chromosome 1q21–23 region (*Fig. 1*). The FRC genes are flanked by the high affinity *FcγRIα* on the centromeric end and the ITAM bearing signaling chain *CD3ζ* on the telomeric end. The telomeric end of the cluster was initially characterized by linkage studies that mapped the location of the low affinity *FcγRII/III* genes to the 1q22–23 region, and studies identified their mouse orthologs in a syntenic region on mouse chromosome 1 (95–98). A more recent analysis of human genomic bacterial artificial chromosome (BAC) clones that overlap this region has clarified the specific gene locations within the low affinity locus (99). The newly defined human Fc receptor related genes, *FcRX/FcRL/FREB* and *FcRY*, are closely linked with the low affinity *FcR* genes and map within 40 kb of *FcγRIIB*. The other classical *FcR* genes, *FcεRIα, and FcγRIα*, and *FcRγc*, the gene for the FcR common gamma chain, reside centromeric of the low affinity *FcγRII/III* genes. Between them lies another recently identified gene, *FcRH6*, which is positioned near a highly related pseudogene (ψ) that shares similar features (our unpublished data). The *FcRH1-5* locus is approximately 2 Mb centromeric of *FcεRIα*, spans more than 300 kb, and is flanked at its telomeric end by a member of the cysteine rich scavenger receptor family, the *5pα* gene. The specific position of *FcγRI* has recently been called into question because of differing placement by genome mapping projects. According to the latest approximation by the National Center for Biotechnology Information (NCBI) we have provisionally placed it in a location that correlates with its original positioning (100, 101).

Homology-based mapping of the human and mouse genomes identifies syntenic regions of human chromosome 1q21–23 that are split between mouse chromosomes 1 and 3. Although the exact boundary between these regions remains unclear, it appears to be centered near the *CD1* locus. *CD1A-E* link within 800 kb centromeric of *FcεRIα*, which is located on mouse chromosome 1, and within 300 kb telomeric of *5pα*, which resides on mouse chromosome 3 (102). Previous work indicates that *CD1* defines a conserved linkage group border between human chromosome 1 and mouse chromosomes 1 and 3 (103, 104). The FRC region has been postulated to be among a group of paralogous *MHC* gene containing regions on chromosomes 1, 6, 9, and 19 that likely emerged through large-scale block duplications (105–107). The location of the genes for the CD1 MHC class I-like molecules, which play their main roles in innate immunity, in the midst of a family of genes that operate at the interface of innate and adaptive immunity, may portend related functions for these paralogous genes.

The 1q21–23 region is a hotspot for translocation events that have been defined in a number of human malignancies (108–111). Some of these translocations affect members of the FRC family, *IRTA1/FcRH4* and *FcγRIIB* (89, 112). Given the location of the mouse chromosome 1 and 3 junction within the FRC and remarkable diversification of the extended Fc receptor family, it is tempting to draw a parallel between the breakpoint of paralogous MHC regions and involvement of these regions in the chromosomal instability and translocations recognized commonly in malignancy. Homology of intergenic elements in these paralogous regions, such as microsatellite repeats, retroelements, and other common repetitive sequences, potentially could provide a framework for promiscuous recombination, which can act as a driving force in natural evolutionary processes and malignant transformation (113–115).

The identification of novel members of the extended FcR

family on mouse chromosomes 1 and 3 helps to refine the definition of mouse and human FRC synteny. The portion of human chromosome 1q21–22 containing *FcγRIα* and *FcRH1-5* is located in a syntenic region of mouse chromosome 3 and is reversed with regard to its human genomic orientation. Characterization of the *moFcRHs* indicates considerable divergence relative to their human counterparts, particularly with respect to the number, order, and chromosomal organization of these genes as well as the location of the *Spα/CD5L/Api6* gene within the *FcRH* locus. Despite inconsistent positioning of these genes, the close linkage of *Spα/CD5L/Api6* in addition to the conserved genomic structure observed among *moFcRH1-3* (our unpublished data) indicates that these mouse genes reside in a syntenic location and share a common ancestry with their human FRC relatives. The location of *FcγRI* telomeric to *moFcRH1-3* not only suggests a common origin for this portion of the extended family, but, along with its linkage to the *FcRHs,* reaffirms the accuracy of its positioning on human chromosome 1q21–22. The location of *CD1D,* centromeric of the *moFcRH* genes, is consistent with its position in humans near the junction between the two FRC derived regions.

The mouse chromosome 1 derived portion of the FRC locus is also in an opposite orientation relative to the syntenic region in humans, but it has generally conserved positioning of its homologous genes. The low affinity *FcγR* genes in this region have been recognized only as single copies in mice compared to their duplicate and diversified relatives in humans. The recent recognition of a third gene proximal to *moFcγRII and moFcγRIII*, *moFcrl3*, indicates another low affinity receptor may exist in mice, and we note that this receptor has greater identity to huFcγRIII (see 'Phylogeny of the extended Fc receptor gene family').

A particularly well conserved feature of FRC genes in both humans and mice is their possession of a split signal peptide encoded by two exons, the first of which most commonly contains both the 5′UTR and translation initiation start site (ATG). The second half of the signal peptide is consistently encoded by a 21 bp exon (97, 100, 116–119). This constitutes an important distinction between the FRC genes and

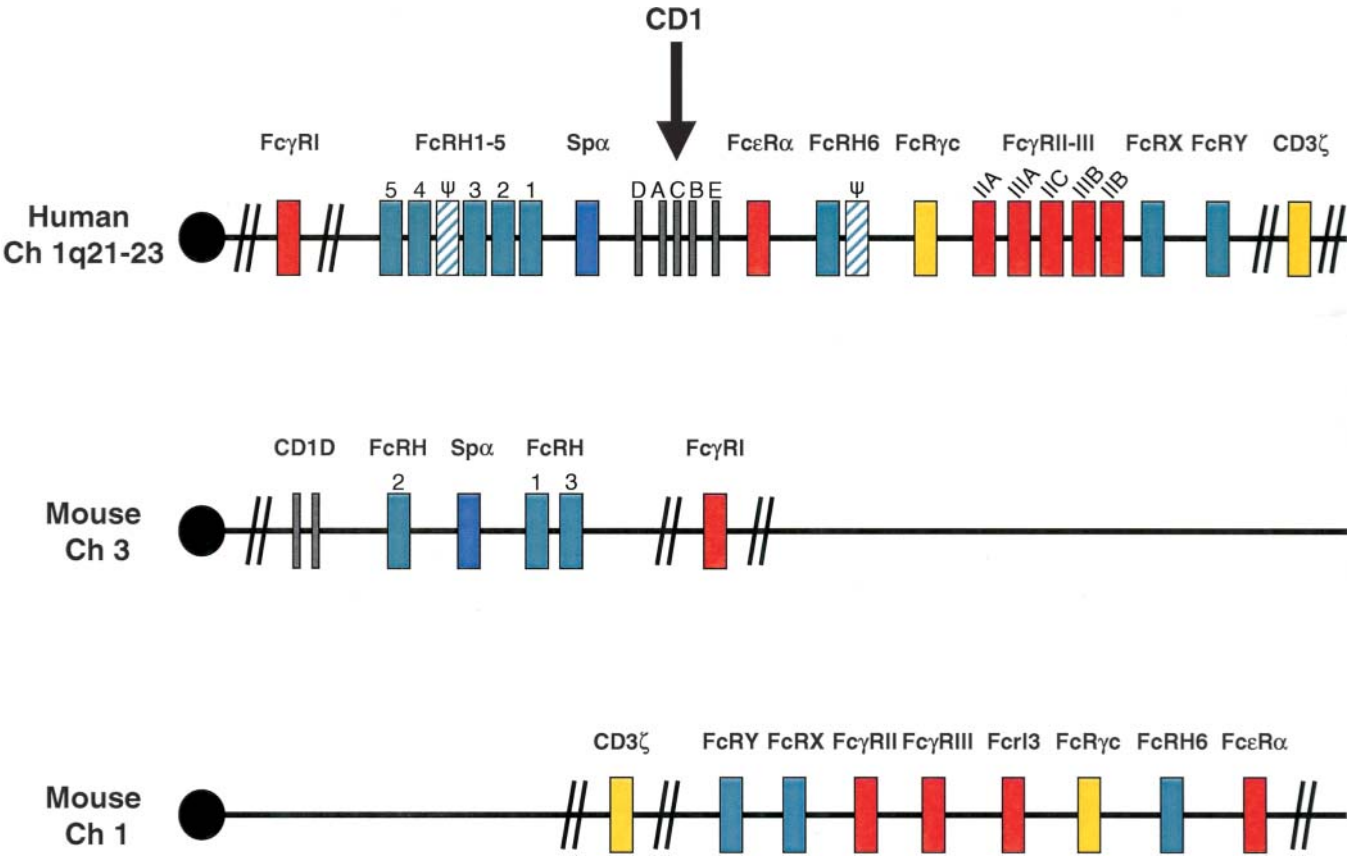


Fig. 1. Organization of the extended FRC gene family in humans and mice. The human 1q21–23 region is depicted along with its syntenic regions located on mouse chromosomes 1 and 3. Approximate positions were determined from NCBI, Celera, Ensembl, Mouse Genome Informatics (MGI) databases, and unpublished observations. Gene positions are approximations and are not to scale.

LRC genes, all of which have a 36 bp second exon (120–123). The extracellular Ig-like domains of all FRC family members are encoded by single exons that follow the phase 1 splicing typical for Ig-like domains (9, 86). A notable exception is the *FcRX* gene, which does not maintain the 21 bp S2 exon, but rather its second exon encodes a partial Ig-like domain that also follows a phase 1 splicing pattern (92). Although the transmembrane and cytoplasmic regions differ widely among FRC family members, the exonic organization among *FcRH* genes is largely conserved (reviewed in 86). *HuFcRH1-5* transmembrane regions are encoded by single exons that are followed by five exons encoding the cytoplasmic tails, the fifth of which includes the translation termination site and the 3′UTR. *HuFcRH6* differs from *huFcRH1-5* in that its cytoplasmic domain is encoded by four rather than five exons (our unpublished data). Highlighting the diversity of the *moFcRHs* is the presence of a seventh exon in one *moFcRH2* isoform that encodes a type B cysteine rich scavenger receptor domain. Notably, this is the first identification of an FRC gene encoding a chimeric molecule containing both Ig-like and cysteine rich scavenger receptor elements. The moFcRH2 scavenger domain is 56% identical to the amino terminal cysteine rich domain of the moSpα/CD5L/Api6 scavenger receptor). This structural feature is not found in any of the huFcRHs or any currently characterized proteins in humans and mice. Other unique features of the extended family are found in the fifth exon of *huFcRX* and *moFcRX*, which encodes a proline and leucine rich domain not seen among other *FcR* or *FcRH* genes. This exon includes the translation termination site and the beginning of the 3′UTR. The classical *FcR* genomic structures have been described elsewhere (9, 10).

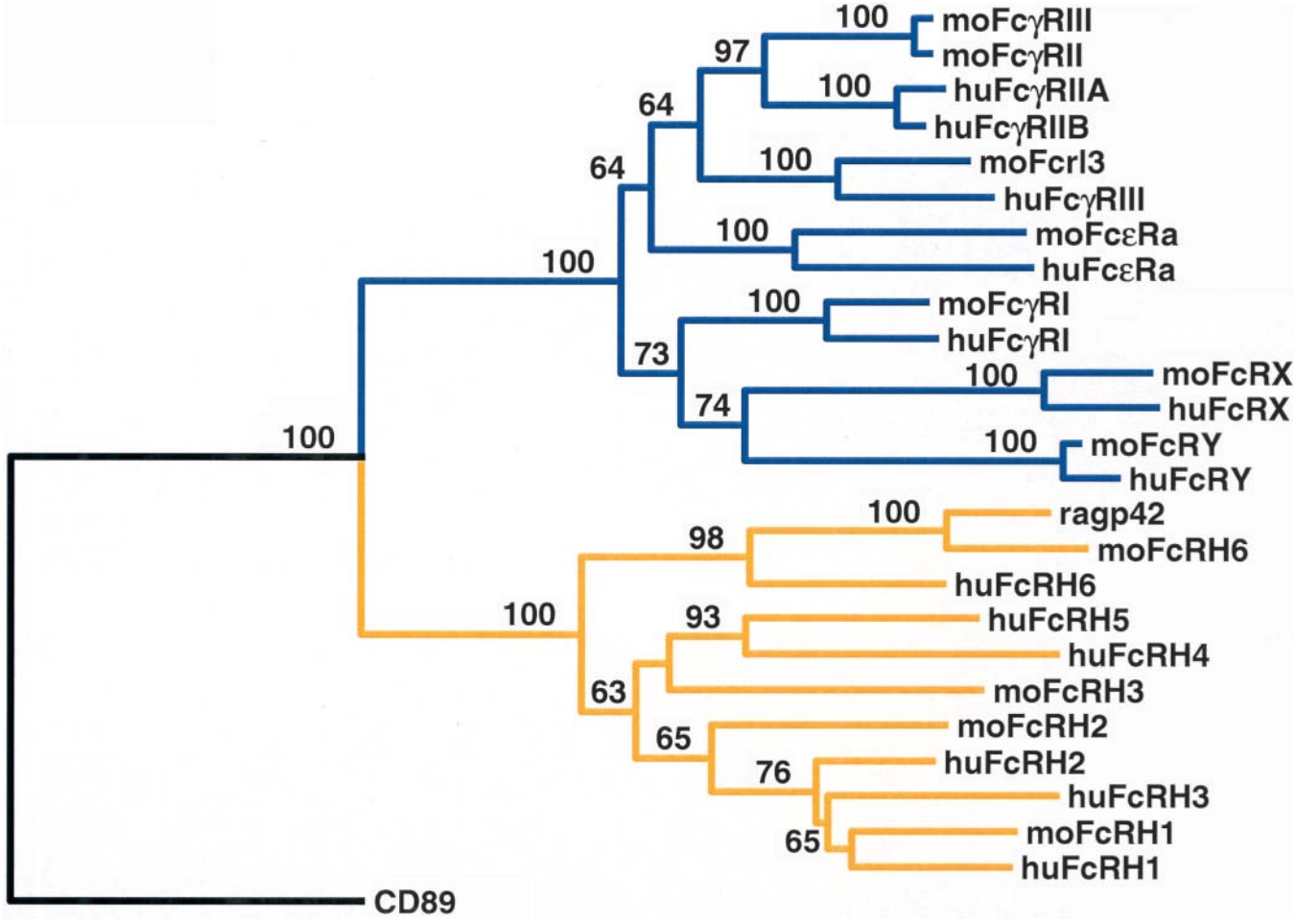
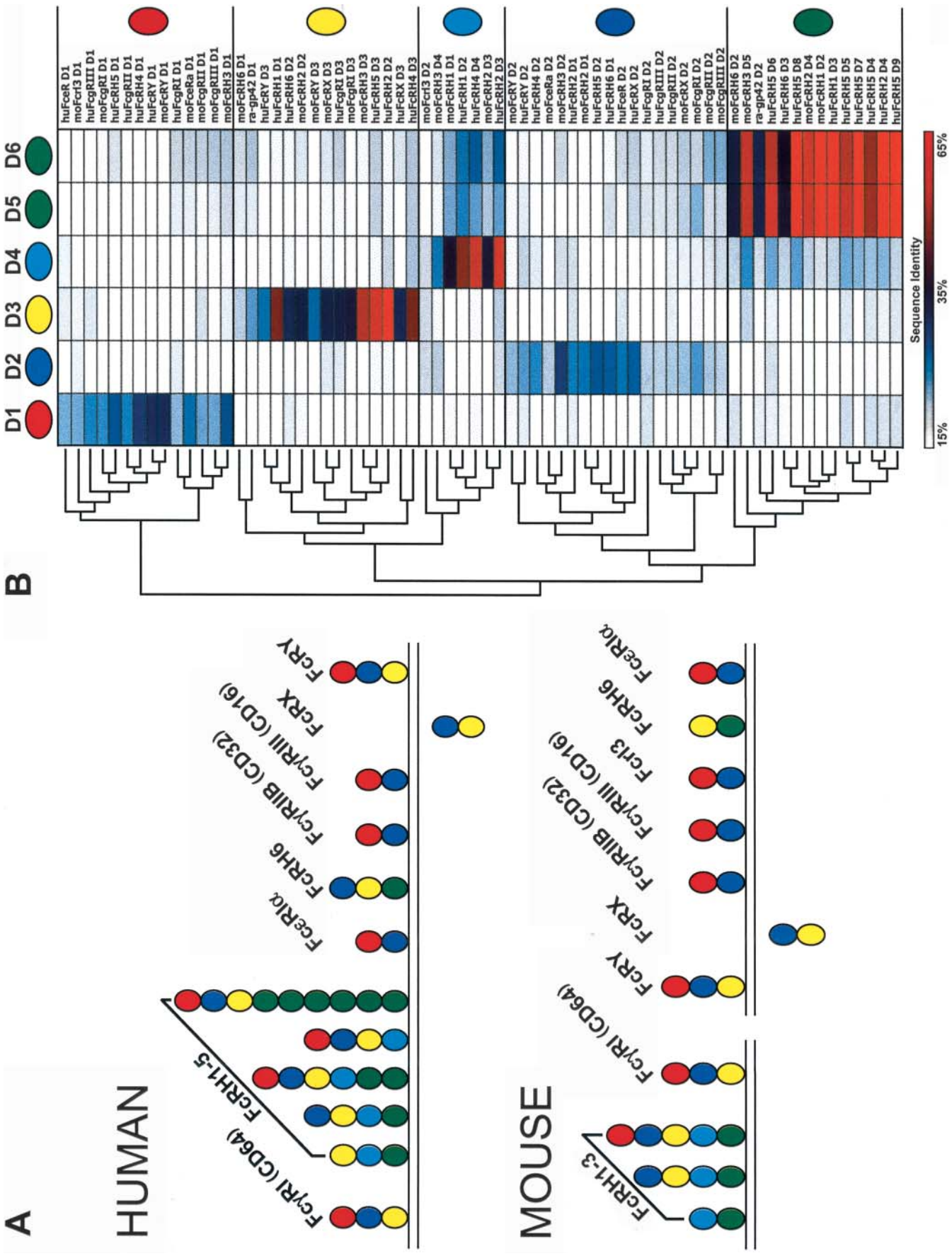


Fig. 2. Phylogenetic relationships of the extended Fc receptor gene family. The extracellular amino acids of each receptor were aligned using ClustalX, and the tree topology was estimated using neighbor-joining where branch values represent percentage bootstrap support after 500 replicates and values below 50% are not shown (47). The chromosome 19 encoded IgA-binding FcαR (CD89) was included in the analysis as a measure of tree topology.

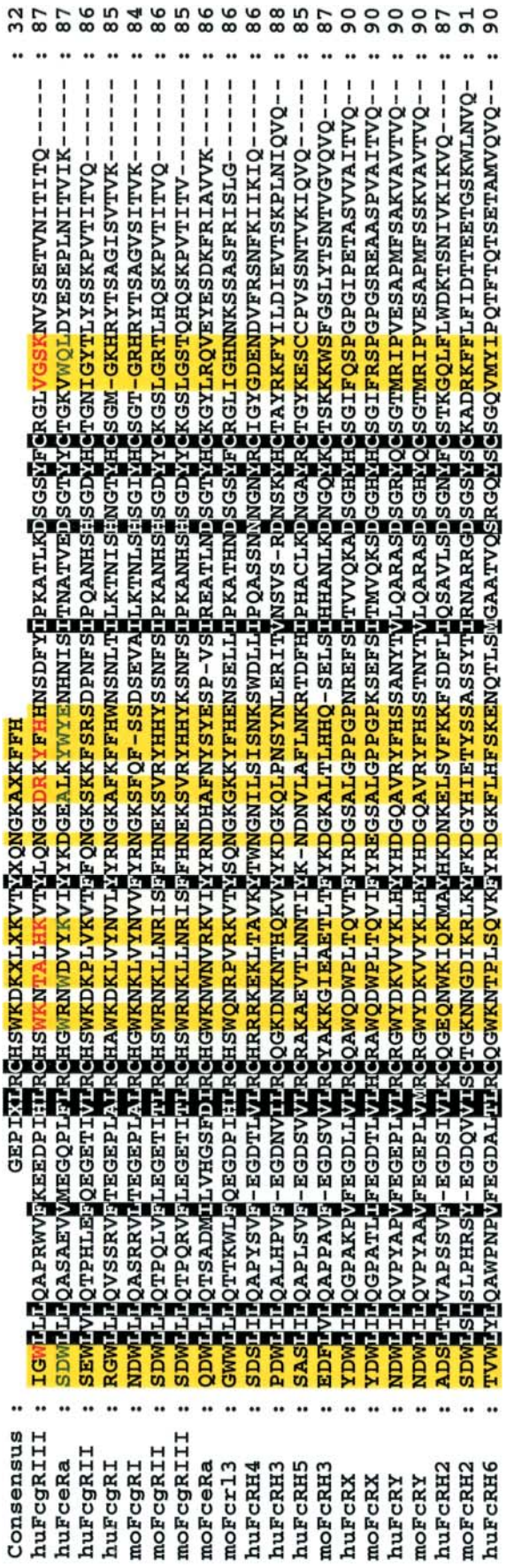

A
HUMAN
FcγRI (CD64)
FCRH1-5
FcεRIα
FCRH6
FcγRIIB (CD32)
FcγRIII (CD16)
FCRX
FCRY
MOUSE
FcγRI (CD64)
FCRY
FCRX
FcγRIIB (CD32)
FcγRIII (CD16)
FcRl3
FCRH6
FcεRIα
FCRH1-3
B
D1
D2
D3
D4
D5
D6
huFceR D1
moFcrl3 D1
huFcgRIII D1
moFcgRI D1
huFcRH5 D1
huFcgRII D1
huFcRH4 D1
huFcRY D1
moFcRY D1
huFcgRI D1
moFceRa D1
moFcgRII D1
moFcgRIII D1
moFcRH3 D1
moFcRH6 D1
ra-gp42 D1
huFcRY D3
huFcRH1 D1
huFcRH6 D2
moFcRH2 D2
moFcRY D3
moFcRX D3
huFcgRI D3
moFcRH3 D3
huFcRH5 D3
huFcRH2 D2
huFcRX D3
huFcRH4 D3
moFcrl3 D2
moFcRH3 D4
moFcRH1 D1
huFcRH1 D2
huFcRH4 D4
moFcRH2 D3
huFcRH2 D3
moFcRY D2
huFcRY D2
huFcRH4 D2
moFceRa D2
moFcRH3 D2
huFcRH2 D1
moFcRH2 D1
huFcRH5 D2
huFcRH6 D1
huFceR D2
huFcRX D2
huFcgRI D2
huFcgRIII D2
huFcgRII D2
moFcRX D2
moFcgRI D2
moFcgRIII D2
moFcRH6 D2
moFcRH3 D5
ra-gp42 D2
huFcRH5 D6
huFcRH6 D3
huFcRH5 D8
moFcRH2 D4
moFcRH1 D2
huFcRH1 D3
huFcRH5 D5
huFcRH5 D7
huFcRH5 D4
huFcRH2 D4
huFcRH5 D9
Sequence Identity
65%
35%
15%

Phylogeny of the extended Fc receptor family

The homology-based identification of multiple human FcR homologs indicates that the regulatory networks involved in modulating cellular function in response to FcR engagement may be surprisingly complex. Their shared chromosomal proximity, genomic structure, and Ig-like domains give credence to the conclusion that the FcR and FcRH gene families are modern descendants of an ancient genetic lineage. The conservation of key cytoplasmic elements involved in intracellular signaling cascades further infers complex biological functions, which may include the modulation of innate and adaptive immune responses. The recent identification of genes encoding additional glycoproteins, *FcRH6*, *FcRX*, and *FcRY*, that share sequence similarity and chromosomal proximity with the *FcR* and *FcRH* gene families indicates that this is a highly dynamic region of the mammalian genome. While FcεRIα, FcRX, and FcRY represent members of the FRC gene family that appear to maintain orthologous relationships in man and mouse, both the *FcR* and *FcRH* families appear to have undergone multiple rounds of gene duplication, exon duplication, and recombination since the speciation of rodent and primate lineages, thereby generating several paralogous receptors (118, 119, 124, 125).

Phylogenetic reconstruction of the extended Fc receptor family based on Ig-like domain amino acid sequences reliably segregates all known syntenic relatives into distinct FcR and FcRH families (*Fig.* 2). Included in this analysis is a novel mouse receptor with significant sequence similarity to huFcγRIII. This receptor, termed moFcrl3 (NCBI Accession: NM_144559), shares a terminal node with huFcγRIII that is segregated from the human and mouse FcγRII genes. Interestingly, the node containing huFcγRIIA, huFcγRIIB, and moFcγRII also includes moFcγRIII, thereby suggesting that the mouse gene currently designated as FcγRIII may actually represent an additional *moFcγRII* gene. Human FcRH6, moFcRH6, ragp42, moFcRH1, and moFcRH2 segregate as new members of the FcRH family, whereas the recently identified FcRX and FcRY relatives cluster with the classical FcRs. While this analysis cleanly separates the *FcR* and *FcRH* gene families into what may be considered distinct genetic lineages, the interdigitating chromosomal arrangement of these families indicates that the *FcR* and *FcRH* families may possess more complex relationships, possibly including genetic recombination between loci. Further evidence suggesting that the *FcR* and *FcRH* loci are actively involved in interlocus recombination comes from comparative analyses of individual Ig-like domains. We have shown that all Ig-like domains in the extended Fc receptor family can be grouped into five domain sub-types based on sequence similarity (85, 86) (*Fig.* 3*A*). Because it possesses all five sub-types of FcR/FcRH extracellular domain sequences, huFcRH3 was used in an all-against-huFcRH3 comparison of individual Ig-like domains to reaffirm the domain designations (*Fig.* 3*B*). Color-coding the extracellular domains of the extended Fc receptor gene family, based on sequence similarity to huFcRH3, depicts a high degree of similarity in domain architecture and highlights at least two possible examples of interlocus recombination events. Notably, domain 3 of huFcRH3 (yellow) represents a subunit that is present in all huFcRH family members, but is unique to huCD64 among the classical FcRs and contributes to its high affinity binding capacity of monomeric IgG (126–128) (see *Fig.* 3*A*). This type of Ig-like domain is also present in both FcRX and FcRY, which appear more closely related to the FcR family based on their chromosomal location and the phylogenetic reconstruction. The degree of genetic complexity emerging as a hallmark feature of the extended FcR gene family is reminiscent of the LRC-encoded multigene families (35), wherein homologous Ig-like receptors exhibit extensive extracellular sequence variation around a common Ig-like structure (59, 129). The core Ig-like structure of LRC encoded receptors is more closely related to the Ig-like domains of FcRs than any other known Ig domain structure and uniquely combines features of both the C2-set and I-set Ig domains (130). Identification of chicken Ig-like receptors (CHIR) that combine features of both the FRC and LRC suggests that the FRC and LRC genes may have belonged to a single gene family as recently as 250 million years ago. Avian homologs, like their mammalian counterparts, exist as paired receptors that share extracellular ligand binding potential but have opposing activating and inhibitory signaling potential. Penetration of these emergent properties into modern avian and mammalian representatives of this ancient genetic lineage attests to the importance of their biological function in vertebrate immunity. In keeping with this conjecture, chro-

Fig.* 3. Conserved extracellular domain architecture. *A) Ig-like domains identified in human and mouse members of the extended Fc receptor family are color-coded based on similarity to huFcRH3 domains. **B)** Heatmap depicting percentage similarities between individual huFcRH3 domains and all other Ig-like domains in the extended Fc receptor family. Sequence similarities were estimated from a Clustal generated all-against-huFcRH3 amino sequence alignment and domains were clustered based on their similarity measures (Spotfire Somerville, MA). Shaded cells represent the degree of similarity between the domain in that row and the FcRH3 domain above that column.



mosomal aberrations involving both the classical FcR and the FcRH gene families have been linked to autoimmunity and malignant transformation. Recently, an epistatic model of interaction between the LRC encoded KIRs and class I MHC alleles has been associated with delayed progression to AIDS in HIV-infected individuals (131).

The second domain of classical FcRs (color coded dark blue) is the major region of Ig–Fc interaction, and this domain clusters with homologous domains from 20 members of the extended Fc receptor family. Based on multiple sequence alignment of the domains designated as dark blue domains in *Fig.* 3*A*, we have identified an Fc-binding consensus sequence that distinguishes this domain from other domains in the extended Fc receptor family (*Fig.* 4, black shading). Notably, this consensus sequence does not include amino acid positions that have been shown to directly interact with Ig–Fc. Perhaps this finding reflects conservation of core residues that are essential for maintaining the structural requirements of Ig–Fc binding, while allowing for variation in the residues that confer ligand specificity (*Fig.* 4, yellow shading). The high degree of variability in the amino acid sequences of domains fitting the Ig-Fc binding consensus correlates with the decreased intensity displayed for the D2 cluster in the heatmap representation of domain similarity in *Fig.* 3B. Correspondingly, while D2 of moFcRL3 possesses the Ig-Fc binding consensus displayed in *Fig.* 4, the amino acid composition of this subunit is equally identical to Ig-like domain subtypes D2–D4, and thus it does not consistently cluster with other domains that match the Ig–Fc binding consensus (*Fig.* 3B). Interestingly, the identification of human cytomegalovirus encoded FcR homologs that bind Ig-Fc, despite their lack of the structural residues described in *Fig.* 4, indicates an unforeseen plasticity in the amino acid sequences that may bestow Ig-binding capability (132).

Diverse signaling potential of FcR family members

Members of the extended FcR family have diverse signaling capabilities based on their possession of tyrosine-based acti-

***Fig.* 4. Sequence similarity predicts Fc-binding potential for several members of the extended Fc receptor family.** Sequences of Ig-like domains clustering with domain 2 (D2) of huFcγRIII and huFcεR were aligned using ClustalX. The original consensus sequence used to identify the human FcR homologs is shown atop the alignment (85). Residues shaded in black represent a consensus sequence that uniquely identifies this cluster of domains and yellow highlights the positions of residues that mediate Fc-binding for huFcγRIII (red letters) and huFcεR (green letters).

vation motifs and/or inhibition motifs that are shared by other activating and inhibitory pairs within the greater immunoreceptor family. The immunoreceptor tyrosine-based activation motifs (ITAM) contain two repeats of the consensus sequence Y-X-X-L/I spaced by 6–8 amino acids (E/D)-X-X-Y-X-X-(L/I)-X_{6-8}-Y-X-X-(L/I), while the immunoreceptor tyrosine-based inhibitory motifs (ITIM) feature a six amino acid consensus sequence (I/V/L/S)-X-Y-X-X-(L/V/I) (63–65, 67, 68). Following ligand binding by the activating receptor complexes, tyrosines in the ITAM are phosphorylated by src family kinases, enabling them to recruit other signaling elements in a signaling cascade that triggers cellular activation. In the case of ITIM bearing receptors, the phosphorylated tyrosines provide a docking site for phosphatases containing SH-2 domains that can abrogate cellular activation via signaling pathways that depend upon tyrosine phosphorylation (133, 134). The balance between activating and inhibitory receptor pairs can thus modulate cellular responses to a variety of stimuli.

The classical receptors FcγRI, FcRγIII (transmembrane form), and FcεRIα have short cytoplasmic tails and transduce activation signals via their non-covalent interaction with the single ITAM bearing FcRγc (79–82, 135, 136); additionally, FcRγIII can also transduce signals via the CD3ζ chain, which possesses three ITAMs (137, 138). The association of receptor subunits is dependent on a single aspartic acid residue present in the transmembrane regions of FcRγc, CD3ζ, FcRγIII, and FcεRIα. This charged residue is the key to the non-covalent interaction of these Fc binding molecules with ITAM bearing co-adapter subunits. The association of FcγRI with the FcRγc subunit occurs via the former's basically charged histidine residue within the transmembrane region. Similar to FcRγIII and FcεRIα, the huFcRH1 transmembrane domain contains an acidic residue (glutamic acid) that could afford interaction with other transmembrane molecules. However, its possession of ITAM-like motifs in its cytoplasmic region suggests that huFcRH1 has autonomous signaling potential, and thus it differs from FcR relatives with short cytoplasmic tails that lack tyrosines. HuFcRH1 may thus be unique in the FcRH family in its possession of both types of immunoreceptor extracellular and adapter subunit characteristics.

In contrast with other classical Fc receptors, the receptors encoded by the *FcγRII* genes do not require co-association with adapter subunits to transduce intracellular signals. They instead possess either cytoplasmic ITAM sequences (FcγRIIA and FcγRIIC) or ITIM sequences (FcγRIIB) with corresponding activating or inhibitory functional capacity. The autonomous signaling property of FcγRII is shared by the FcRHs that possess ITIMs, ITAMs, or both types of signaling motifs in their cytoplasmic tails (*Table 1*). The ITIMs found in the FcRH cytoplasmic tails maintain residues of the (I/V/L/S)-X-Y-X-X-(L/V/I) consensus motif. Tyrosine motifs present in some FcRH cytoplasmic domains share the previously defined ITAM consensus (E/D)-X-X-Y-X-X-(L/I)-X_{6-8}-Y-X-X-(L/I). For example, huFcRH1, huFcRH3, and moFcRH1 generally follow this defined motif. Other ITAM-like sequences are found among the FcRH cytoplasmic domains that maintain analogous positional conservation of tyrosine residues, but differ slightly in amino acid character at the +3 position. Although these sequences are highly reminiscent of ITAMs, functional studies will be required to clarify their functionality. Other tyrosine based motifs found in huFcRH1 and huFcRH3, may constitute 'hemi-ITAMs', wherein the sequence (E/D)-X-X-Y-X-X-(A/V) is present but a tandem second tyrosine-based sequence is not. A similar motif is noted in PIR-B (49).

Clearly the FcRHs are likely to differ substantially in their signaling capabilities relative to those of the FcR family members. Conversely, a signaling role is unlikely in the case of FcRX, since it does not possess a transmembrane region or N-linked glycosylation sites. Rather, its acidic biochemical characteristics are consistent with the likelihood that it functions intracellularly, perhaps as a scaffolding component interacting via its Ig-like domains. The evolutionary origins of the tyrosine-based functional capacities of the FcRHs versus those of its classical FcR relatives are not obvious. However, it is clear that similar tyrosine-based motif complexity is shared among FcRH family members. This may imply that the intracellular signaling elements engaged by these receptors will be shared among FcRHs, but may differ from those currently defined for other tyrosine-based immunoreceptors. The presence of both ITIM and ITAM in the same cytoplasmic tail adds complexity to their signaling potential. This signal transduction potential coupled with Ig-binding capacity of some FcRHs may involve new cellular signaling pathways.

Polymorphism of the Fc receptor family

The classical human receptors FcγRIIA and FcγRIIB are expressed in several distinct splice variant isoforms. In addition, FcγRI, FcγRII (A, B and C) and FcRγIII (A, transmembrane; and B, glycosylphosphatidylinositol (GPI)-anchored form) each have naturally occurring allelic variants that reflect non-synonymous single nucleotide polymorphisms (SNPs). The SNPs in the second extracellular domain (D2) of FcγRIIA and FcγRIIIA affect Fc binding affinity and specificity, while the

non-synonymous transmembrane SNP in FcγRIIB alters receptor signaling (R.P.K. unpublished results, 139). The short cytoplasmic tails of both FcγRIA and FcγRIIIA modulate signal transduction through non–covalent association with FcRγc (140, 141), but the impact of the cytoplasmic sequence variants of FcγRIA and FcγRIIIA on the transduction of activation signals has not been established (142). Both the FcRγc and CD3ζ signaling partners of the FcRs appear to be invariant (143, 144).

Not surprisingly, members of the *FcRH* family may also display both splice variant and allelic diversity, the full extent of which has yet to be elucidated. Several splice variants have been reported that modify the open reading frame. These include two potentially secreted variants and a GPI anchored form of *IRTA2* (*FcRH5*) (89) and a truncated form of *FcRH2* (91). Multiple splice variants, including a D2-deficient sequence of *FcRH4*, have been identified on a message level (our unpublished results). Corresponding FcRH protein isoforms have not yet been characterized, but the existence of at least some of these isoforms would parallel structural themes established for the classical FcRs. The frequency of SNPs in the *FcRH* coding regions is consistent with many other human genes (145). *FcRH3* has one non-synonymous SNP in the D1 extracellular domain ($Asn^{28} \rightarrow Asp^{28}$) and a second non-synonymous SNP in the cytoplasmic domain ($Pro^{660} \rightarrow Leu^{660}$) that modifies a candidate ITAM motif. The latter SNP occurs with an allele frequency of 0.01 in Caucasians versus an allele frequency of 0.16 in the African-American population. This difference, coupled with similar allele frequencies in the two groups for the D1 SNP, is consistent with differential evolutionary pressure on the corresponding function. Unlike the classical *FcR*, however, *FcRH3*-5 do not appear to have SNPs that affect amino acid sequence in the second extracellular domain (A.W.G. and R.P.K. unpublished results). *FcRH4* has a synonymous T>C transition at nucleotide 516 in D2 ($Glu^{172} \rightarrow Glu^{172}$), but a second putative non-synonymous entry in

***Table 1.* Activating and inhibitory tyrosine-based signaling motifs**

Receptor	ITAM-like	ITIM	Other tyrosines
huFcRH1	EFTYLNSPTPGQLQPIYENV DIYSRLRKANITDVDYEDA		SGDEVYSLAYYNQPEQ
huFcRH2	EFTYSSPTPDMEELQPVYVNV	VVYSQV VIYSSV	
huFcRH3	EPMYSNVNPGDSNPIYSQI	VLYSEL	EDDEENYENVPRV
huFcRH4		SLYVDV LVYSEI VVYSEV	
huFcRH5	EPTYHNVPAWEELQPVYTNA	VVYSEV IIYSEV	
huFcRH6		VVYSVV	GEQCPLYANVHHQ
moFcRH1	EPLYENVNVVSGNEVYSLV		VLQGSTYPKSPDS QVSSGLYSKPRIN NIAHMDYEDAM
moFcRH3	EPTYYNVPACIELQPVYSNE	VIYTEV	
huCD32A	DGGYMTLNPRAPTDDDKNIYLTL		EETNNDYETADGG
huCD32B		ITYSLL	ISALPGYPECREM
moCD32B		ITYSLL	PEEVGEYRQPSGL(B1) PTSSSPYNPPDLE(B1) EETEHDYQNHI
huFcRγc	DGVYTGLSTRNQETYETL		
moFcRγc	DAVYTGLNTRSQETYETL		
huCD3ζ	NQLYNELNLGRREEYDVL EGLYNELQKDKMAEAYSEI DGLYQGLSTATKDTYDAL		
moCD3ζ	NQLYNELNLGRREEYDVL EGVYNALQKDKMAEAYSEI DGLYQGLSTATKDTYDAL		

Tyrosines and key positional residues of the ITAM and ITIM consensus motifs are underlined.

GenBank (C536T which changes $Ser^{179} \rightarrow Leu^{179}$) has not been identified in the sequence analysis of *FcRH4* in 48 African-Americans and 50 Caucasians.

The mouse ortholog of *FcRH3* may also exist in polymorphic forms. Analysis of spleen mRNA from five inbred mouse strains indicates the existence of two alleles, one that is expressed in BALB/c, 129, CBA, and NZB mice and the other in C57BL/6 mice. The nucleotide discrepancies between the two forms result in peptide sequences that vary by the insertion or deletion of one residue and by single residue differences at nine other positions. These polymorphisms, located in the extracellular portion of the moFcRH3 protein, affect three of the four most amino-terminal Ig domains, namely D2, D3, and D4. One of the polymorphic residues creates a site for N-linked glycosylation in one allele only, and five of the residue differences, including the insertion, are situated among highly conserved residues in the portion of the peptide that is within the D2-Fc binding region of classical Fc receptors (dark blue domains *Fig. 3A*). The locations of these polymorphic residues suggest they could affect ligand binding.

Conclusion

The chromosome 1q21–23 region contains two related families of genes, the classical *FcR* (*FcγRI*, *FcγRII*, *FcγRIII*, and *FcεRI*) and the *FcRH* genes. The former have been shown to provide a structural basis for the molecular interaction between immune effector cells and the antibodies of the humoral immune system. This interaction results in phagocytosis, inflammatory responses, and the regulation of antibody production. The recent identification of the Fc receptor homologs promises to significantly expand this biological field of study. The diversity of structural features and signaling potentials of FcR/FcRH family members indicate an unanticipated complexity for the ligand-binding and functional repertoire of this extensive immunoreceptor family. The wealth of knowledge already accumulated for the classical FcRs will fuel the future biological definition of these new family members and broaden our understanding of the functional roles for this diverse family of molecules in host defense.

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